

### **REMARKS**

Applicant respectfully requests reconsideration. Claims 1-5, 7-20 and 27-41 were previously pending in this application. Claim 1 has been amended to indicate that the filter with a low capacity for protein adsorption is a cellulose acetate or nitrocellulose filter. Support for the amendment can be found at least at claim 7 and at page 13, lines 6-7 of the specification as originally filed. Claim 13 has been amended to replace the word “comprises” with the word “comprise” to correct the grammatical error. Claim 7 has been cancelled because “cellulose acetate” limitation of claim 7 has been added to claim 1. Claims 8-11 have been amended to remove dependency from now-cancelled claim 7. As a result, claims 1-5, 8-20, and 27-41 are pending for examination with claims 1 and 13 being independent claims. No new matter has been added.

### **Allowable Subject Matter**

Claims 13-16 and 31-41 have been allowed.

### **Rejections under 35 U.S.C. §112**

The Examiner rejected claims 1-5, 7-12, 17-20, and 27-30 under 35 U.S.C. §112, second paragraph as being indefinite. Applicants have amended claim 1 to indicate that the filter with a low capacity for binding protein is a cellulose acetate filter or a nitrocellulose filter. Applicants submit that one of ordinary skill in the art would recognize that cellulose acetate filters have a low capacity for binding protein. In addition, one of ordinary skill in the art would be able to use information readily available from a filter manufacturer to select a commercially available nitrocellulose filter with a low protein-binding capacity and to use such a filter in the methods as claimed.

Accordingly, withdrawal of the rejection of claims 1-5, 8-12, 17-20, and 27-30 under 35 U.S.C. §112 is respectfully requested.

### **Rejections Under 35 U.S.C. §103**

The Examiner rejected claims 1-5, 7-12, 17-20, and 27-30 under 35 U.S.C. §103(a) as being unpatentable over Notario et al., Archivio per le scienze mediche, 135(1):1-8 (1878 Jan-Mar) [Abstract] in view of Mueller (U.S. Patent No. 4,094,775) or Gokcen (U.S. Patent No. 6,428,785) and in further view of Kalchman et al. (WO 97/18825). Applicants respectfully traverse the rejection.

To support a *prima facie* case for obviousness, the Examiner must demonstrate motivation to combine the teachings in the references to make the claimed invention, a reasonable likelihood of success in making the combination of references, and that the references teach every element of the claimed invention. Applicants submit that these requirements for a *prima facie* case of obviousness have not been met.

The Examiner interprets the Notario abstract as teaching “contacting a sample material having protein aggregates from membrane proteins after solubilization by urea or detergent, sodium dodecyl sulphate (SDS) with a cellulose acetate filter” and that “(P)rotein aggregates on the cellulose acetate filter are subjected to hemoglobin electrophoresis for detection of membrane proteins”. In contrast, Applicants submit that the Notario abstract describes routine electrophoretic separation of proteins along a cellulose membrane, which is not a method of filtering insoluble from soluble proteins in a solubilized sample. The Notario abstract does not teach a method of solubilizing a solution that includes proteins and filtering the solution through a filter to retain insoluble proteins and to allow to pass soluble proteins.

With respect to the Mueller et al. reference, the Examiner states that Mueller discloses that cellulose acetate membrane filters are used in filtration methods for capturing or retaining (preventing passage of) very large protein molecules and cellular constituents. Applicants respectfully point out the Mueller et al. reference at col. 4, lines 30-34 indicates that the filter does not allow the passage of “very large molecules such as proteins and cellular constituents of the blood”. Applicants submit that Mueller et al does not teach or suggest use of a filter to separate insoluble from soluble proteins – but rather suggests use of a filter to prevent passage of large molecules, including proteins.

With respect to the Gokcen et al reference, Examiner states “Gokcen discloses that cellulose acetate and polysulfone membrane filters are low protein binding filter membranes used in filtration methods for capturing or retaining insoluble protein aggregates.” Applicants submit that the Gokcen reference mentions filtering to sterilize a pharmaceutical solution and minimize risks to a patient posed by “insoluble particulates or microaggregates”, and suggests that the use of a polysulfone filter is preferable to use of a cellulose acetate filter for the filtration.

With respect to the Kalchman et al reference, the Examiner indicates that Kalchman identifies the insoluble proteins HIP1 and huntingtin protein and separates them for visualization, and states at page 6 of the Office Action that Klachman uses a “filter device in capturing and isolating large insoluble proteins.” Applicants submit that Kalchman et al. reference does not teach or suggest use of a filter device but rather describes the use of electrophoretic methods to separate insoluble proteins (HDI1 and huntingtin) from each other followed by blotting of the separated proteins onto a PVDF membrane for detection of the proteins in separate locations on the membrane. The Kalchman does not teach or suggest use of a filtration method to separate insoluble from soluble proteins.

Applicants submit that the Examiner has not indicated specific motivation for one of skill in the art to combine the references in the manner that is suggested. Applicants also contend that even if the teachings of the cited references were combined, the combination would not result in the claimed invention. The Examiner states at page 5, paragraph 1 that “Mueller discloses that cellulose acetate membrane filters are used in filtration methods for capturing or retaining (preventing passage of) very large protein molecules and cellular constituents.” Applicants respectfully point out that although Mueller does describe a filtration system that allows a solvent and substances in normal molecular solution in the solvent to pass through, Mueller specifically states at col. 4, lines 30-34 that the filter does not allow the passage of “very large molecules such as proteins and cellular constituents of the blood”. Applicants submit that Mueller et al does not teach or suggest use of a filter to separate insoluble from soluble proteins – but rather suggests use of a filter to prevent passage of large molecules, including proteins, whether soluble or not. Mueller’s purpose is dialysis filtration of blood. Thus, Mueller does not

teach or suggest filtration of a solubilized solution through a filter to separate insoluble from soluble proteins from the solution.

At page 5, first paragraph of the Office Action, the Examiner states “Gokcen discloses that cellulose acetate and polysulfone membrane filters are low protein binding filter membranes used in filtration methods for capturing or retaining insoluble protein aggregates.” Applicants respectfully point out that Gokcen does not specifically mention filtering for capturing or retaining of insoluble *proteins* but suggests the use of polysulfone filters to sterilize a pharmaceutical solution through removal of “insoluble particulates or microaggregates”. The cited passage additionally suggests that it is preferable to use polysulfone membranes rather than cellulose acetate membranes for this purpose.

Applicants submit that neither Notario et al. nor Kalchman et al. teaches or describes any filtration method and neither discloses or suggests filtration of a solubilized sample through a filter to separate insoluble from soluble proteins. Thus, the combination of the cited references accordingly does not provide the claimed invention.

Applicants submit that the Examiner has not shown any specific motivation for one of ordinary skill in the art to combine the teaching of the cited references to make the claimed invention and that one of ordinary skill in the art would have no reasonable expectation of success in making the combination of references.

The Examiner states at page 6 of the Office Action that “it would have been obvious to one of ordinary skill in the art at the time of the instant invention to have substituted cellulose membrane filters as taught by Notario as modified by Mueller or Gokcen into the filtering device used in the method of Kalchman in capturing and isolating the large insoluble proteins or amyloid-like fibrils such as HIP1 and huntingtin.” Applicants submit one would not have been motivated to substitute cellulose membrane filters as taught by Notario and modified by Mueller or Gokcen, because Notario does not teach cellulose membrane as a filter but rather discloses a standard use of a cellulose membrane for electrophoretic separation. Applicants provide herewith an online publication from Sigma-Aldrich (St. Louis, MO) that describes the separation of hemoglobin proteins using cellulose acetate electrophoresis, which is the method described in the Notario et al. abstract. Applicants submit that a cellulose membrane disclosed by Notario et

al. is not used or suggested for use as a filter. Electrophoresis of hemoglobin proteins on cellulose acetate, as disclosed in the Notario abstract, does not involve filtering a sample through a filter or use of the cellulose acetate as a filter, but rather includes loading a sample onto a piece of cellulose acetate membrane and the application of an electric current to induce differential migration of proteins in the sample along the horizontal plane of the membrane. The Notario abstract does not teach or suggest the use of cellulose acetate as a filter. The Notario abstract also does not teach or suggest filtration of a sample through a filter to retain and capture insoluble protein aggregates and fibril and to pass solubilized fibrils and proteins.

The Examiner states at page 6 of the Office Action that one of ordinary skill in the art would substitute a cellulose membrane filter taught by Notario into the “filtering device used in the method of Kalchman”. As described above, Applicants assert that Notario fails to describe a filter or use of a filtration. Applicants additionally submit that Kalchman does not disclose a filtering device. The Kalchman et al. publication describes separation procedures used to assess the relationship and interactions between insoluble huntingtin proteins and insoluble HID1 proteins. In Example 8, at page 16, Kalchman describes immunoprecipitation procedures for HID1 and huntingtin proteins. The immunoprecipitation methods disclosed include, in part, preparing a tissue lysate, incubating the lysate with anti-huntingtin antibodies, separating the lysate-antibody mixture on an SDS-PAGE gel, transferring the PAGE-separated proteins onto a PVDF membrane, and contacting the membrane with anti-huntingtin and anti-HID1 antibodies to detect the presence of the two separated proteins. Kalchman does not disclose the use of filtration or a filtering device. Rather, Kalchman uses SDS-PAGE electrophoresis to separate the insoluble huntingtin and HID1 proteins and simply blots the separated proteins onto a PVDF membrane for detection of the two separated proteins. In contrast to the Examiner’s contention, Kalchman does not set forth a filtration procedure and the substitution of a cellulose acetate membrane into the procedures disclosed by Kalchman would not result in the claimed invention.

Applicants submit that the Examiner has not indicated a specific motivation to combine the cited references to make the claimed invention. Neither Notario nor Kalchman teach or suggest a method that includes filtering but instead use routine electrophoretic methods to separate individual proteins from each other, followed by standard membrane blotting of the separated proteins. The Examiner has not set forth specific motivation to modify the methods of

Notario or Kalchman to use a very different method of separating soluble and insoluble proteins by filtration – especially in light of the fact that filtering through cellulose acetate filter would not yield the results sought by Notario or Kalchman in their disclosures. The Notario and Kalchman methods are each designed to allow separation of individual proteins followed by blotting of all of the separated proteins onto the surface of a membrane for detection of the individual proteins independent from each other. Filtration of a sample through a membrane as in the instantly claimed methods would not be suitable for the separations of either Kalchman or Notario because the instantly claimed filtration methods would not allow separation of different proteins on the surface of a membrane. Thus, Applicants submit that one would have no motivation to combine the teachings of Notario, Kalchman and the other references cited to make the claimed invention.

In summary, Applicants submit that there is no specific motivation to combine the references to make the claimed invention, and even if the teaching of the references were combined, it would not result in the invention as claimed. Thus, the Examiner's burden to set forth a *prima facie* case for obviousness has not been met. Accordingly, reconsideration and withdrawal of the rejection of claims 1-5, 7-12, 17-20, and 27-30 under 35 U.S.C. §103(a) as being unpatentable over Notario et al., Archivio per le scienze mediche, 135(1):1-8 (1878 Jan-Mar) [Abstract] in view of Mueller (U.S. Patent No. 4,094,775) or Gokcen (U.S. Patent No. 6,428,785) and in further view of Kalchman et al. (WO 97/18825) is respectfully requested.

**CONCLUSION**

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,  
*Erich Wanker et al., Applicant(s)*

By:



Helen C. Lockhart, Ph.D.

Reg. No. 39,248

Wolf, Greenfield & Sacks, P.C.

600 Atlantic Avenue

Boston, Massachusetts 02210-2206

Telephone: (617) 646-8000

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